REMARKS

Claims 1-3 and 5-14 are pending in the Application. Claim 13 was amended herein to correct a typographical error in the spelling of "zona pellucida." Applicants respectfully assert that the recitation of pending claims in the Office Action, i.e., claims 1-14, is incorrect. Claim 4 was cancelled in Applicants' Amendment of August 8, 2002. Subsequently, in an Advisory Action mailed September 23, 2002, the Examiner indicated that the Amendments had been entered. Therefore, claim 4 stands cancelled. Clarification is respectfully requested.

The pending claims stand variously rejected. Each rejection is respectfully traversed as discussed below. Applicants respectfully submit that the claims are in condition for allowance and earnestly solicit notification to that effect.

Rejections Withdrawn

Applicants wish to thank the Examiner for indicating that the rejections of claim 1 and 12 under 35 USC §112, first paragraph and 35 USC §102(b), respectively, have been withdrawn.

Rejection under 35 U.S.C. § 102(b)/§ 103

Claims 12 and 14 stand rejected as anticipated under 35 U.S.C. § 102(b), or in the alternative, under 35 U.S.C. § 103 as obvious over Gurdon (J. Cell Sci. Suppl. 4; 287-318 (1986)). This rejection is respectfully traversed.

In the Office Action dated October 3, 2001, the Examiner remarked that the patentability of a product-by process claim is determined by the novelty and nonobviousness of the product itself without consideration of the process for making it recited in the claims. However, MPEP 2113 states:

> The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where...the manufacturing steps would be expected to impart distinctive structural characteristics to the final product.

MPEP 2113, citing *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979).

Claims 12 and 14 are drawn to embryos made by the method of claim 1 (claim 12) or 13 (claim 14). The method steps of claims 1 and 13 necessarily result in embryos having

"distinctive structural characteristics," namely, bovine cytoplasm and non-bovine nuclear DNA.

As acknowledged by the Examiner, Gurdon reviews the state of the art of nuclear transfer and specifically teaches nuclear transfer of one amphibian species to an enucleated oocyte of a second amphibian species. Nevertheless, the Examiner asserts that the general disclosure on page 312 regarding "the early success of nuclear transfer in mammals," (citing the work of Illmensee & Hoppe and Kelly & McGrath) encompasses the instantly claimed nuclear transfer embryos because bovines are mammals. Therefore, the Examiner's position appears to be that the work done with nuclear transfer mouse embryos reviewed by Gurdon would inherently possess the characteristics of the embryos of claims 12 and 14. Applicants respectfully disagree that the disclosure of Gurdon regarding intraspecies nuclear transfer experiments in mice teaches or suggests even mammalian trans-species nuclear transfer, much less embryos having bovine cytoplasm and non-bovine DNA.

Applicants respectfully submit that the embryos of claims 12 and 14 are structurally distinguishable from embryos obtained by intraspecies nuclear transfer because both the embryo according to claim 12 and the embryo according to claim 14 would retain bovine cytoplasmic characteristics and non-bovine nuclear characteristics. In this regard, the Examiner is directed to Campbell *et al.* (cited in the Office Action) regarding intraspecies nuclear transfer embryos: "In the true sense of the meaning these individuals [created by nuclear transfer techniques] would not be clones as unknown cytoplasmic contributions in each may vary and also the absence of any chromosomal rearrangements would have to be demonstrated." (Campbell et al, page 2, lines 1-5.) Clearly, if the intraspecies nuclear transfer embryos discussed in the cited references exhibit these structural differences from "normal" embryos, the claimed trans-species embryos would certainly exhibit structural differences that would reflect their trans-species character.

Moreover, because the cytoplasm is contributed by the donor bovine oocytes, the claimed embryos retain bovine mitochondrial DNA and the nuclear DNA of a species other than bovine, in stark contrast to an intraspecies nuclear transfer embryo, which would have mitochondrial and nuclear DNA of a single species. It is well established that mammalian oocytes contribute mitochondrial DNA to the developing embryo and that maternally-derived mitochondrial DNA persists, and in fact, predominates, from fertilization through maturity. The Examiner is again respectfully invited to review the article entitled "Dolly is not quite a clone," from the August 1999 issue of Nature Science Update (http://www.nature.com/nsu/990902/990902-5.html), which was originally submitted with

the Response filed August 8, 2002. Applicants submit that an embryo at any stage of development made according to claim 12 would be distinct from an embryo obtained by intraspecies nuclear transfer because it would have bovine mitochondrial DNA and nuclear DNA from a species other than bovine, and would not, therefore, be the same as an embryo obtained by intraspecies nuclear transfer. Thus, the embryos of claims 12 and 14 are not anticipated by Gurdon.

Moreover, Applicants respectfully submit that the embryos of claims 12 and 14 are not obvious over the teachings of Gurdon. *Prima facie* obviousness requires: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings; 2) a reasonable expectation of success; and 3) all of the claimed limitations must be taught or suggested by the references. MPEP 2142.

As argued above, all the limitations of the embryos of claims 12 and 14 are not taught or suggested by Gurdon. Specifically, Gurdon does not teach an embryo having bovine cytoplasm and non-bovine nuclear DNA. Gurdon does not even teach an embryo having mammalian cytoplasm from one species and nuclear DNA from a second mammalian species. Despite the extensive review of trans-species nuclear transfer experiments in amphibians, there is no suggestion in Gurdon to even experiment with trans-species nuclear transfer using <u>any</u> mammal, much less bovine/non-bovine combinations.

The First Declaration, originally submitted in the Response filed November 12, 2002, states, "Gurdon teaches that development beyond the maternal to embryonic transition of amphibians reliably occurs if the nuclear transfer donor cell is from a pregastrula or pre-maternal to embryonic stage, but not if the donor cell is at the gastrula stage or has undergone maternal to embryonic transition. The maternal to embryonic transition of amphibians occurs at the twelfth cell cycle, whereas that of cattle and sheep occurs at the third cell cycle, that of primates and swine occurs at the second cell cycle, and that of rodents in the first cell cycle. Because of the differences in embryo development with respect to mechanisms, genomic imprinting, role of maternal cytoplasm, maternal control of positioning of cells in the embryo, and the like, the amphibian is not considered a good or true developmental model for mammals. The amphibian studies would not be expected to predict the outcome of trans-species nuclear transfer into mammalian oocytes, especially using bovine oocytes. Gurdon cites the work of Brun, who introduced a mammalian donor cell into an amphibian oocyte and produced a cleavage stage embryo, which did not pass the maternal to embryonic

transition in development of either the donor or recipient species. Activation of an oocyte that had not received a donor nucleus would also result in a cleavage stage embryo."

Accordingly, claims 12 and 14 are not anticipated or obvious over Gurdon. Applicants respectfully request reconsideration and allowance of these claims.

Rejection under 35 U.S.C. § 102(e)

Claims 12 and 14 stand rejected under 35 U.S.C. § 102(e) as anticipated by Stice *et al.* (WO 95/17500). The rejection is respectfully traversed.

Stice *et al.* teach nuclear transfer procedures for producing transgenic ungulate animals using blastomeres from fertilized embryos as a nuclear transfer donor and transgenic embryonic stem cell derived nuclear transfer embryos.

As argued above, the method steps of claims 1 and 13 necessarily result in embryos having distinctive structural characteristics, namely, bovine cytoplasm (having bovine mitochondrial DNA) and non-bovine nuclear DNA. Applicants respectfully submit that embryos having these characteristics are not taught by Stice *et al.*

The Examiner has characterized Stice *et al.* as teaching that "various combinations of species can be done." However, Applicants have reviewed Stice *et al.*, and were unable to find any discussion of trans-species nuclear transfer, i.e., use of an enucleate oocyte of one species and an NT donor of another species. Under the Field of Invention, at page 1, lines 19-23, Stice *et al.* teach producing chimeric ungulate embryos made by introducing blastomeres obtained from a fertilized embryo into a nuclear transfer embryo produced using an embryonic stem cell as a donor. Although "chimeric" is not expressly defined in Stice *et al.*, it is clear from the disclosure that Stice *et al.* did not use the word "chimeric" to refer to a nuclear transfer embryo made from two different species of organisms (see, e.g., discussion on page 15, lines 1-15, wherein chimeric is described in the context of chimeric offspring produced "by combining tetraploid mouse embryos with mouse embryonic stem cells"). In Example 5, the only one of the Examples that mentions "chimeric embryos," a chimeric embryo is said to be produced by transferring "two blastomeres from an 8-16 cell stage fertilized embryo into the perivitelline space of an eight to 16-cell embryonic stem cell clone." There is no mention of using two different species in any aspect of the method, let alone any discussion of a nuclear transfer embryo made from two different species.

The Examiner's attention is directed to the steps of the methods disclosed by Stice *et al.* A comparison of the steps of the disclosed method of nuclear transfer (beginning at page 16, line 13 of Stice *et al.*) with those of the disclosed method of producing non-human

chimeric embryos (beginning at page 17, line 3 of Stice *et al.*) reveals that the only difference is that the latter method includes step (vii), which involves introducing one or more blastomeres into the perivitelline space of the cultured nuclear transfer embryo, but Stice *et al.* does not teach using two different species to make the nuclear transfer embryo of steps (i)-(vi). In other words, a nuclear transfer embryo made by steps (i)-(vi) is used in step (vii) to make a chimeric embryo by introducing a blastomere into the perivitelline space of the cultured nuclear transfer embryo.

Furthermore, the chimeric embryos made by embryonic transplantation or by splitting and recombining embryos, as described in Stice, would have a nucleus with chromatin from two different sources. In contrast, the nuclear transfer embryo of the present invention would have only the nuclear chromatin of the nuclear donor cell.

Because Stice *et al.* does not teach an embryo according to claims 12 or 14, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-14 stand rejected under 35 U.S.C. § 103 as obvious over a combination of Prather *et al.*, Gurdon, Campbell *et al.*, Telford *et al.*, Dominiko *et al.* and Stice *et al.* The rejection is respectfully traversed.

Applicants respectfully remind the Examiner that a *prima facie* rejection under § 103 is not established if all elements of the claimed invention are not taught or suggested by the references. MPEP 2143. *See also Rockwell International Corp. v. United States*, 147 F.3d 1358, 1365 (Fed. Cir. 1998).

Applicants maintain that even when the references cited by the Examiner are taken together, all elements of the presently claimed invention are not taught or suggested. Moreover, even a combination of the references does not provide any teaching or suggestion that would motivate one of skill in the art to add the missing elements to arrive at the claimed invention. Given the glaring deficiencies of the references vis-à-vis all elements of the claimed invention, there is also no reasonable expectation of success. *Cf. Rockwell*, 147 F.3d at 1365.

Each of the pending claims require the use of a non-bovine donor cell and a bovine recipient oocyte. None of the cited references teach or suggest these elements. As discussed above, Gurdon reviews trans-species nuclear transfer experiments with respect to combinations of various amphibian species. Gurdon's discussion of nuclear transfer experiments with respect to mammals does not teach or suggest trans-species nuclear transfer

using recipient bovine oocytes. The First Declaration points out differences between amphibian and bovine oocytes that render the ability to obtain a trans-species nuclear transfer embryo by nuclear transfer into an enucleated bovine oocyte unpredictable and non-obvious.

Similarly, Stice *et al.* does not include any discussion of trans-species nuclear transfer, i.e., use of an enucleate oocyte of one species and an NT donor of another species, much less methods of producing embryos from enucleated bovine oocytes and non-bovine nuclear donors.

The Examiner agrees that Prather *et al.* does not teach trans-species nuclear transfer, but states that "each of Gurdon, Prather *et al.* and Stice *et al.* teach that nuclear transfer is possible using mammalian material." Applicants do not dispute that intra-species nuclear transfer has been accomplished in various species of mammals. However, the claimed invention requires trans-species nuclear transfer using enucleated bovine oocytes, which is not taught or suggested by any of the cited references.

The Office Action further states that Cambpell *et al.* provides a recent status of nuclear transfer techniques, and in particular, the use of donor cells that have been arrested in G_0, maturation curves for bovine oocytes and activation of the NT unit. Similarly, the Office Action states that Dominko *et al.* and Telford *et al.* provide guidance for the optimization of use of bovine oocytes. However, none of these references supply the missing limitations of the claimed invention.

Despite the key deficiencies in the cited references, the Office Action states, "the bovine oocyte, like the amphibian oocyte has certain capacities to support growth of a NT unit made by transpecies nuclear transfer." However, as this statement is not attributed to any reference, it appears that the Examiner has impermissibly used the present application as a "blue print" for the rejection.

The Examiner states that "Gurdon teaches that the more related the oocyte recipient/nuclear transfer unit species is phylogenetically, the better able is the resulting NT unit to be cultured." Applicants note Gurdon states that "the nucleus of one species with the cytoplasm of another is nearly always lethal; the more distantly related the species, the earlier does development arrest." However, this statement does not amount to a suggestion to attempt trans-species nuclear transfer embryos in closely related mammalian species. Moreover, one of skill in the art would certainly not have a reasonable expectation of successfully producing the claimed trans-species embryos based on the teachings of Gurdon. As recognized by the Examiner, Gurdon notes at page 312 that there are special difficulties

that seem to afflict nuclear transplantation in mammals, which actually leads the skilled artisan away from the claimed invention.

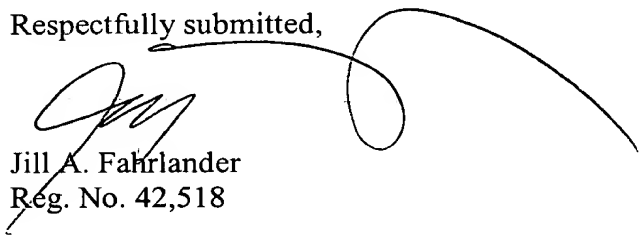
Moreover, in the discussion of the references at pages 9-11 of the Office Action, there appears to be some confusion regarding the terms "chimeric," "transgenic" and "trans-species," as these terms are used interchangeably. However, Stice *et al.* is the only cited reference to utilize the term "chimeric." As discussed above, a chimeric embryo is taught by Stice *et al.* to be produced by transferring "two blastomeres from an 8-16 cell stage fertilized embryo into the perivitelline space of an eight to 16-cell embryonic stem cell clone." "Transgenic," as used in the art and the cited references means "referring to an organism that contains a foreign gene." Concise Dictionary of Biomedicine and Molecular Biology, 2d Ed., P. Juo (CRC Press 2002). Neither "chimeric" nor "transgenic" refers to an embryo produced using an oocyte of one species as a recipient and a nuclear donor from another species.

Because the cited references, taken alone or in combination, do not teach or suggest all required elements of claims 1-14, do not teach or suggest modifying the references to arrive at the claimed invention, and provide no reasonable expectation of success, withdrawal of the rejection under 35 USC § 103 is respectfully requested.

CONCLUSION

In view of the foregoing, reconsideration and allowance of claims 1-3 and 5-14 is respectfully requested. The Examiner is strongly encouraged to contact the undersigned by telephone at the Examiner's convenience should any issues remain with respect to the Application.

Respectfully submitted,



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